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May 5, 1993

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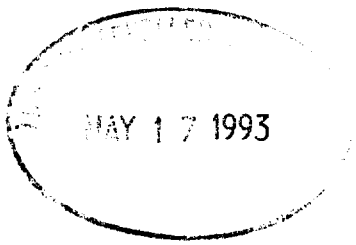

Dear Dr. Lederberg:

Thank you for your reply to my fax which will now enable me to send you a proper letter and the documentation.The direct reply to your inquiry is that there have been no subsequent studies on using the Shope papilloma virus as a means of gene therapy for arginase deficiency. I believe that the consensus amongst workers in the field that there is no arginase gene encoded in this chromosome.We now know the entire gene compliment of the Shope papilloma virus and all of the open reading frames are accounted for. I suppose, in principle, there may be another gene hidden in an anti-sense chain, but this is doubtful. Thus, there is no basis for continuing.

Soon after I entered the arginase field, my attention was drawn to this most spectacular series of papers and the possibilities that this might present for the field. As I began to work on the arginase protein and realize how difficult the protein chemistry was, the less plausible many of these ideas became. Eventually, there were so many implausibilities, so many impossibilities, and the irreproducibility of the studies, that I began to believe that this work was either incredibly incompetent or else it was completely manufactured. My opinion was in no way altered by the fact that I had heard subsequently that Rogers was a peculiar character, was quite a loner and my in fact have had a drinking problem.

I did not have time to review all of the papers meticulously, but let me give you some examples of published items that disturb me greatly. In his early papers he reports the amino acid content of different Shope papilloma viruses and also the impact of the ground up papilloma on added arginine in the medium. He reports that the arginine level goes to 0. Those of us who work with any of the arginases know that because the Km and Ki for ornithine are so close, that the reaction can never go to completion despite the exeryonic nature. The reaction almost always stops at 50%. In fact, during our assay we try never to utilize more than 5 or 10% of the substrate in order to get an accurate idea of the activity. Secondly, as soon as you become involved in this work you realize that there is probably no way in hell that 3g of papilloma tissue could yield enough arginase to be purified to homogeneity and to allow an amino acid analysis to be done. Bear in mind that this work was done nearly 30 years ago, the extraction and purification methods

were much more crude and Rogers himself was not a protein chemist and probably would not have the skills to do this with hundreds of times more material. Thirdly, he has rather absurd specific activities for arginase in liver and in fibroblasts. I believe that the difference between normal fibroblasts and horse liver were a factor of 2-3. In reality, normal fibroblasts probably have no arginase activity, if they do it is very low amounts of the second isozyme of arginase and a quantitation would have to be hundreds of times less than in liver. He said that he could dilute the fibroblast extract 100 times and get activity. Other workers have got to use undiluted fibroblasts, let the reaction go for 16 hours or more and then still do not get any meaningful activity.

Two other aspects of virology also impress me. Firstly Satoh *et al.* and Orth *et al.* failed to be able to find any difference between liver arginase and the arginases of the papilloma. In this same regard, he reports that a host range mutant of the Shope papilloma virus causes a different arginase to be made Even at that time, one should have been able to infer that a host range change probably altered a receptor or a recognition for the virus and that a change in the properties of an enzyme, and a radical change at that, was probably not likely to occur.

In summary then, this body of work reflects a poor understanding and mastery of virology, a poor understanding of the known enzymology of the arginases (Greenberg and his colleagues have done much of the early and quite accurate work on the enzyme in mammals) and if I am right a reckless disregard for honesty and for the safety of patients. Although I never met the man and I bear him no ill will, I have to conclude that the deviation from the known facts of the enzymology are so great that it is possible that the entire story was largely manufactured. Along with this research, I have been able to ascertain just how relatively low the standards were for acceptance to what now are major journals. A number of papers concerning arginase have appeared in Nature and none of them would have been considered publishable by even the most obscure journals today. I realize that this was nearly 30 years ago, but I am aware of numerous papers that I read in any number of journals that were absolute classics. The standards were not universally lower in the past.

I look forward to hearing your own conclusions about this issue. If you are able to draw ones radically different from my own I would be delighted to be challenged and to understand your reasons for doing so.

With best wishes.

Sincerely yours,

Stephen Cederbaum, M.D.
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